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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 October 2000 (16.10.00)	
International application No. PCT/EP00/00957	**Applicant's or agent's file reference** FC 864
International filing date (day/month/year) 07 February 2000 (07.02.00)	**Priority date** (day/month/year) 17 February 1999 (17.02.99)
Applicant PAMPARANA, Franco	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 September 2000 (06.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year) 31 March 2000 (31.03.00)	
Applicant's or agent's file reference FC 864	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/00957	International filing date (day/month/year) 07 February 2000 (07.02.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 17 February 1999 (17.02.99)
Applicant PHARMACIA & UPJOHN S.P.A. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
17 Febr 1999 (17.02.99)	MI99A000313	IT	21 Marc 2000 (21.03.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

P. Regis

Telephone No. (41-22) 338.83.38

WO 00/48592
PCT/EP00/00957

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 24 August 2000 (24.08.00)	
Applicant's or agent's file reference FC 864	**IMPORTANT NOTICE**
International application No. PCT/EP00/00957	**International filing date** (day/month/year) 07 February 2000 (07.02.00)
Priority date (day/month/year) 17 February 1999 (17.02.99)	
Applicant PHARMACIA & UPJOHN S.P.A. et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EA,EE,EP,ES,FI,GB,GD,GE,GH,
   GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,
   PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   24 August 2000 (24.08.00) under No. WO 00/48592

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Continuation f Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
24 August 2000 (24.08.00)	
Applicant's or agent's file reference	**International application No.**
FC 864	PCT/EP00/00957

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 16 October 2000 (16.10.00)	
Applicant's or agent's file reference FC 864	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/00957	07 February 2000 (07.02.00)	17 February 1999 (17.02.99)

Applicant
PHARMACIA & UPJOHN S.P.A. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BR,BY,CH,CU,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,
   HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,
   TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Olivia TEFY

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
31 March 2000 (31.03.00)	
Applicant's or agent's file reference	**International application No.**
FC 864	PCT/EP00/00957

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

PHARMACIA & UPJOHN S.P.A. (for all designated States except US)
PAMPARANA, Franco (for US)

International filing date	:	07 February 2000 (07.02.00)
Priority date(s) claimed	:	17 February 1999 (17.02.99)
Date of receipt of the record copy by the International Bureau	:	21 March 2000 (21.03.00)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [X] confirmation of precautionary designations
- [ ] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

P. Regis

Telephone No. (41-22) 338.83.38

ANNEX TO FORM PCT/IB/301

International application No.
PCT/EP00/00957

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PCT EPO - DG 1

08. 02. 2000

REQUEST

(46)

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 0 0 / 0 0 9 5 7
International Application No.

(07. 02. 2000) 07 FEB 2000
International Filing Date

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) FC 864

Box No. I TITLE OF INVENTION

ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PHARMACIA & UPJOHN S.p.A.
Via Robert Koch 1.2
20152 Milano
Italy

☐ This person is also inventor.

Telephone No.
0039 02 4838.1

Facsimile No.
0039 02 4838.2734

Teleprinter No.

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Franco Pamparana
Piazza Firenze, 19
20100 Milano
Italy

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is,country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PHARMACIA & UPJOHN S.p.A.
Patent Department
Viale Pasteur, 10
20014 Nerviano (Milano)
Italy

Telephone No.
0039 02 4838.5409

Facsimile No.
0039 02 4838.5397

Teleprinter No.

☒ **Adress for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

PCT/EP 00/00957

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*.

Regional Patent

+ TZ, Tanzania + Co/E

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH** and **LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AE** United Arab Emirates
- ☒ **AL** Albania
- ☒ **AM** Armenia
- ☒ **AT** Austria
- ☒ **AU** Australia
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria
- ☒ **BR** Brazil
- ☒ **BY** Belarus
- ☒ **CA** Canada
- ☒ **CH and LI** Switzerland and Liechtenstein
- ☒ **CN** China
- ☒ **CU** Cuba
- ☒ **CZ** Czech Republic
- ☒ **DE** Germany
- ☒ **DK** Denmark
- ☒ **EE** Estonia
- ☒ **ES** Spain
- ☒ **FI** Finland
- ☒ **GB** United Kingdom
- ☒ **GD** Grenada
- ☒ **GE** Georgia
- ☒ **GH** Ghana
- ☒ **GM** Gambia
- ☒ **HR** Croatia
- ☒ **HU** Hungary
- ☒ **ID** Indonesia
- ☒ **IL** Israel
- ☒ **IN** India
- ☒ **IS** Iceland
- ☒ **JP** Japan
- ☒ **KE** Kenya
- ☒ **KG** Kyrgyzstan
- ☒ **KP** Democratic People's Republic of Korea .....
- ☒ **KR** Republic of Korea
- ☒ **KZ** Kazakhstan
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MD** Republic of Moldova
- ☒ **MG** Madagascar
- ☒ **MK** The former Yugoslav Republic of Macedonia .....
- ☒ **MN** Mongolia
- ☒ **MW** Malawi
- ☒ **MX** Mexico
- ☒ **NO** Norway
- ☒ **NZ** New Zealand
- ☒ **PL** Poland
- ☒ **PT** Portugal
- ☒ **RO** Romania
- ☒ **RU** Russian Federation
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia
- ☒ **SK** Slovakia
- ☒ **SL** Sierra Leone
- ☒ **TJ** Tajikistan
- ☒ **TM** Turkmenistan
- ☒ **TR** Turkey
- ☒ **TT** Trinidad and Tobago
- ☒ **UA** Ukraine
- ☒ **UG** Uganda
- ☒ **US** United States of America .....
- ☒ **UZ** Uzbekistan
- ☒ **VN** Viet Nam
- ☒ **YU** Yugoslavia
- ☒ **ZA** South Africa
- ☒ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn bythe applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 17.02.1999 17 February 1999	MI99A000313	IT ~~Italy~~		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	3
description (excluding sequence listing part)	:	6
claims	:	3
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	13

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: accompanying letter

Figure of the drawings which should accompany the abstract:

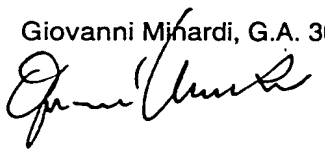
Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

PHARMACIA & UPJOHN S.p.A.

Giovanni Minardi, G.A. 36668



For receiving Office use only

1. Date of actual receipt of the purported international application:	07 FEB 2000 (07.02.2000)	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 864		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/00957	07/02/2000	17/02/1999
International Patent Classification (IPC) or national classification and IPC A61K31/23		
Applicant PHARMACIA & UPJOHN S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/09/2000	26.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Escolar Blasco, P Telephone No. +49 89 2399 7331

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/00957

I. Basis f the r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-6	as originally filed	

Claims, No.:

1-9	with telefax of	07/02/2001

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description,	pages:	
☒ the claims,	Nos.:	10-29
☐ the drawings,	sheets:	

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations
see separate sheet

Comm nts on it m V

1. Reference is made to the following documents:

   D1: US-A-5 760 081
   D2: E.SWAHN Et al.: 'Omega-3 ethyl ester concentrate decreases total apolipoprotein CIII and increases antithrombin III in postmyocardial infarction patients' CLINICAL DRUG INVESTIGATION, vol. 15, no. 6, 1998, p. 473-82

2. Having regard to the present prior art the subject-matter of claims 1-9 seems to be novel, since none of the documents cited in the search report describes the use of a mixture with high concentration of EPA and DHA to be administered orally for preventing mortality in postmyocardial infarction patients:

2.1 D1 refers to a method for preventing imminent ventricular fibrillation in post-myocardial infarction patients by infusing a mixture of EPA and DHA. Oral administration is not disclosed.

2.2 D2 refers to the oral administration of a mixture with 85% content in EPA+DHA in postmyocardial infarction patients. A teaching regarding the suitability of this mixture for preventing mortality can however not be found in this study.

2.3 Other documents classified as X in the ISR do not seem to refer specifically to postmyocardial infarction patients; therefore, they are not relevant for the assessment of the novelty of present claims 1-9.

3. The subject-matter of claims 1-9 appears to involve an inventive step, the reasons being as follows:

   Neither D1 nor D2 provide the solution (of claim 1) to the problem of how to prevent mortality in patients having suffered from myocardial infarction. D2 is regarded as the closest prior art with respect to the subject-matter of claim 1. The data disclosed in D2 would prompt the skilled person to conclude that a mixture

with high concentration of EPA and DHA to be administered orally is not useful in preventing mortality of postmyocardial infarction patients, as the increased level of LDL cholesterol is directly related to the risk of myocardial infarction (see p.481, left col. second paragraph).
The suitability of such a mixture for decreasing mortality is however shown by the clinical trial cited in the present description.

3.1 All other claims are allowable.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
FC 864		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 00957	07/02/2000	17/02/1999
Applicant		
PHARMACIA & UPJOHN S.P.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/00957

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/23 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 760 081 A (A.LEAF, H.HALLAQ) 2 June 1998 (1998-06-02) claims 1,2,4 column 1, line 16-24 column 2, line 12-14 column 5, line 20-28 column 7, line 56-61 column 8, line 9-14 --- -/--	1,2,8,9, 12,18, 24,27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 753 703 A (C.CAVAZZA, M.CALVANI) 19 May 1998 (1998-05-19) claims 1,3,4,8 column 1, line 10-20 column 3, line 66 -column 4, line 2 column 4, line 16-19	1,2,5,8, 9,11,12, 15,18, 21,24, 26,27,29
X	GB 2 218 984 A (RENAFIELD) 29 November 1989 (1989-11-29) claims 1,4,6-10,15-17 page 17, line 12-24	1-5, 8-15, 18-21, 24-29
X	CHEMICAL ABSTRACTS, vol. 122, no. 8, 20 February 1995 (1995-02-20) Columbus, Ohio, US; abstract no. 89398, PAN YUZHEN, LIU RONGKUI, LIU ZHE: "soft capsules containing ethyl docosahexanoate and other ingredients for use as antithrombotic and antidementia agents" XP002139955 abstract	1,2,5,8, 9,11,12, 15,18, 21,24, 26,27,29
X	& CN 1 082 909 A (PEOPLES REPUBLIC OF CHINA) 2 March 1994 (1994-03-02)	
X	E.SWAHN E.A.: "Omega-3 ethyl ester concentrate decreases total apolipoprotein CIII and increases antithrombin III in postmyocardial infarction patients" CLINICAL DRUG INVESTIGATION, vol. 15, no. 6, 1998, pages 473-482, XP000914344 page 473 page 474 page 481, column 1	1,2,5,8, 9,11-13, 15,18, 19,21, 24-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/00957

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5760081 A	02-06-1998	NONE	
US 5753703 A	19-05-1998	IT RM950835 A	23-06-1997
		CA 2191645 A	22-06-1997
		EP 0780124 A	25-06-1997
		JP 9176005 A	08-07-1997
GB 2218984 A	29-11-1989	AT 75502 T	15-05-1992
		CA 1334207 A	31-01-1995
		CN 1040050 A,B	28-02-1990
		DE 68901382 D	04-06-1992
		WO 8911521 A	30-11-1989
		EP 0409903 A	30-01-1991
		ES 2017268 A	16-01-1991
		GR 89100345 A	10-10-1991
		PT 90668 A,B	30-11-1989
CN 1082909 A	02-03-1994	NONE	

AMENDED CLAIMS

1. Use of essential fatty acids containing a mixture of eicosapentanoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction where the content in EPA+DHA in such mixture is greater than 25% b.w, and the medicament is for oral administration.

2. Use according to claim 1, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

3. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

4. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is about 85% b.w.

5. Use according to claim 4, wherein the medicament is for oral administration, at a dosage from about 0.7 g to about 1.5 g daily.

6. Use according to claim 5, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

7. Use of essential fatty acids containing eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction, wherein the EPA or DHA content is greater than 25% b.w.; and the medicament is for oral administration.

8. Use according to claim 7, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

9. Use according to claim 7 or 8, wherein the EPA or DHA content is from ab ut 60 to about 100% b.w.

CLAIMS

1. Use of essential fatty acids containing a mixture of eicosapentanoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction where the content in EPA+DHA in such mixture is greater than 25% b.w.

2. Use according to claim 1, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

3. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

4. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is about 85% b.w.

5. Use according to anyone of claims 1 to 4, wherein the medicament is for oral administration.

6. Use according to claim 4, wherein the medicament is for oral administration, at a dosage from about 0.7 g to about 1.5 g daily.

7. Use according to claim 6, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

8. Use of essential fatty acids containing eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction, wherein the EPA or DHA content is greater than 25% b.w.

9. Use according to claim 8, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

10. Use according to claim 8 or 9, wherein the EPA or DHA content is from about 60 to about 100% b.w.

11. Use according to anyone of claims 8 to 10, wherein the medicament is

for oral administration.

12. A method for preventing mortality in a patient who has survived a myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) wherein the content in EPA+DHA in such mixture is greater than 25% b.w.

13. A method according to claim 12, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

14. A method according to claim 12, wherein the content in EPA+DHA in such mixture is about 85% b.w.

15. A method according to claim 12, 13 or 14, wherein the medicament is administered orally.

16. A method according to claim 14, wherein the medicament is administered orally at a dosage from about 0.7g to about 1.5 g daily.

17. A method according to claim 16, wherein the EPA/DHA ratio in the EPA+DHA mixture is about 0.9/1.5

18. A method for preventing sudden death in a patient, who is survivor of myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (DPA) and docosahexaenoic acid ethyl ester (DHA), wherein the content in EPA+DHA in such mixture is greater than 25% b.w.

19. A method according to claim 18, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

20. A method according to claim 18, wherein the content in EPA+DHA in such mixture is about 85% b.w.

21. A method according to claim 18,19 or 20, wherein the medicament is

administered orally.

22. A method according to claim 20, wherein the medicament is administered orally at a dosage from about 0.7g to about 1.5 g daily.

23. A method according to claim 22, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

24. A method for preventing morality in a patient who has survived a myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or in docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

25. A method according to claim 24, wherein the contention EPA or DHA is form about 60 to about 100% b.w.

26. A method according to claim 24 or 25, wherein the medicament is administered orally.

27. A method for preventing sudden death in a patient who is survivor of myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

28. A method according to claim 27, wherein the content in EPA or DHA is from about 60 to about 100% b.w.

29. A method according to claim 27 or 28, wherein the medicament is administered orally.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/23, A61P 9/10

A1

(11) International Publication Number: **WO 00/48592**

(43) International Publication Date: 24 August 2000 (24.08.00)

(21) International Application Number: PCT/EP00/00957

(22) International Filing Date: 7 February 2000 (07.02.00)

(30) Priority Data:
MI99A000313 17 February 1999 (17.02.99) IT

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I–20152 Milano (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: PAMPARANA, Franco [IT/IT]; Piazza Firenze, 19, I–20100 Milano (IT).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS

(57) Abstract

The invention concerns the use of essential fatty acids with a high content in eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) or a high concentration mixture thereof in the preparation of a medicament useful for preventing mortality, in particular due to sudden death, in patients who have suffered from a myocardial infarction.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

"ESSENTIAL FATTY ACIDS IN THE PREVENTION OF CARDIOVASCULAR EVENTS"

DESCRIPTION

This invention concerns the use of a pharmaceutical composition containing essential fatty acid ethyl esters originating from fish oils, in particular as a high concentration mixture of ethyl esters of (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in the prevention of cardiovascular events, especially of mortality in patients who have survived the hospitalization phase of acute myocardial infarction (AMI).

It is well known that certain essential fatty acids contained in fish oil have a therapeutic effect in the prevention and treatment of cardiovascular disorders, such as in the treatment of thrombosis, hypercholesterolemia, arteriosclerosis, cerebral infarction and hyperlipemias.

U.S. Patents US 5,502,077, US 5,656,667 and US 5,698,594 can be quoted as examples.

From the above prior art, it is known in particular the utility of fatty acids belonging to the ω-3 family, more specifically (20:5ω 3) eicosapentaenoic acid (EPA) and (22:6ω 3) docosahexaenoic acid (DHA) in treating the above-mentioned disorders.

Indeed EPA, being a precursor of PGI3 and TxA3, exerts a preventing platelet aggregation effect and an antithrombotic effect that can be ascribed to inhibition of cyclooxygenase (similar effect to that of aspirin) and/or to competition with arachidonic acid for this enzyme, with consequent reduction in the synthesis of PGE2 and TxA2, which are well known platelet aggregating agents.

On the other hand DHA is the most important component of cerebral lipids in man and furthermore, being a structural component of the platelet cell,

it intervenes indirectly in increasing platelet fluidity, thus playing an important role in antithrombotic activity.

International patent application W089/11521, whose description is herein incorporated by reference, describes in particular an industrial process for extracting mixtures with a high content in poly-unsaturated acids, including EPA and DHA and their ethyl esters, from animal and/or vegetable oils.

Mixtures of fatty acids, especially EPA/DHA, obtained according to W089/11521, are reported to be particularly useful in the treatment of cardiovascular diseases.

However, currently used treatments in human therapy have been shown to be insufficient in preventing cardiovascular events, and more specifically mortality, in particular due to sudden death, which happen in patients who have had a myocardial infarction, on account of recurrences after a first acute myocardial infarction episode.

Therefore, there still is the need for an effective drug, in particular for preventing these recurrences.

Object of this invention, therefore, is the use of essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, in the preparation of a medicament useful for preventing mortality, due, for instance, to cardiovascular events or sudden death, in patients who have suffered from a myocardial infarction.

According to a preferred aspect this invention therefore provides the use of essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof, in the preparation of a medicament useful for preventing sudden death in patients who have suffered from a myocardial infarction.

For ease of description "EPA-ethyl ester" and "DHA-ethyl ester" will be also quoted here as "EPA" and "DHA".

An essential fatty acid with high content in EPA-ethyl ester or DHA-ethyl

ester, according to the present invention, preferably contains more than 25% by weight (b.w.), in particular from about 60 to about 100% of such ester.

These compounds can be obtained by known methods.

In an essential fatty acid with a high concentration mixture of EPA-ethyl ester and DHA-ethyl ester, preferably such mixture has a content in EPA + DHA greater than 25% by weight, in particular from about 30 to about 100% by weight, preferably about 85% by weight.

In the EPA/DHA mixture, EPA preferably is present in a percentage from about 40 to about 60% by weight and DHA, preferably in a percentage from about 25 to about 45-50%.

In any case the preferred EPA/DHA ratio in such EPA/DHA mixture is about 0.9/1.5.

PHARMACOLOGY

The efficacy of the treatment, according to the invention, is, for instance, proven by the fact that a surprising and highly significant reduction in post-infarction mortality was observed by such treatment in a clinical trial that lasted for 3.5 years, with protocols substantially designed as follows:

1 a "control " group received the standard therapy which is usually given to infarcted patients;

2 a "treatment" group, besides the therapy that was given to the "control" group, received 85% EPA+DHA (1 g daily);

3 a "treatment" group, besides the therapy that was given to the "control" group received vitamin E; and

4 a "treatment" group, besides the therapy that was given to the control group, received vitamin E and 85% EPA+DHA (1 g daily).

In fact the group of patient "treated" according to protocol 2 showed, in comparison to "control" group 1, a decrease of about 20% in total

mortality, with a decrease of about 40% of mortality due to sudden death and a notable reduction in mortality due to other cardiovascular events.

On the contrary, no significant results were achieved in group 3 as compared to the control group 1, whereas there was a reduction in total mortality of about 19% in group 4 as compared to the control group, with results that were similar to those obtained in treated group 2.From the above clinical results, the person skilled in the art will appreciate that, the use of a pharmaceutical composition in accordance to the present invention is certainly useful in human therapy in preventing mortality in patients who have suffered from a myocardial infarction.

Accordingly, this invention provides a method for preventing mortality in a patient who has survived a myocardial infarction, comprising administering to such patient a therapeutically effective amount of a medicament containing essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof.

As known, sudden death is an important contributor to the mortality rate in patients with cardiac disease, accounting for over 450,000 death per year in the USA.

About 80% of such patients, particularly those survivors of acute myocardial infarction with low ventricular ejection fractions, are at high risk of sudden death or reinfarction.

The above clinical results show that the present invention provides a new and valuable therapeutic tool for preventing sudden death in patients in particular in those who survived acute myocardial infarction.

Accordingly, as a preferred aspect, the present invention also provides a method for preventing sudden death in a patient, who is survivor of myocardial infarction, comprising administering to such patient a therapeutically effective amount of a medicament containing essential fatty acids with a high content in EPA-ethyl ester or DHA-ethyl ester or a high concentration mixture thereof.

The essential fatty acids, according to the invention, can either have a high content, for instance more than 25% b.w., in EPA-ethyl ester or DHA-ethyl ester or in a mixture thereof. However EPA-ethyl ester and DHA-ethyl ester are preferably present as a mixture thereof with a content in EPA+DHA higher than 25% b.w, in particular from about 30 to about 100% b.w., preferably about 85% b.w.

Based on the obtained clinical results, according to a preferred aspect of the invention, the dosage of an essential fatty acid containing a EPA+DHA mixture with 85% b.w. titer for oral administration to a patient may vary from about 0.7 g to about 1.5 g daily, preferably about 1 g daily.

This amount of product as EPA+DHA mixture (or amount of EPA-ethyl ester alone or DHA-ethyl ester alone) may be administered in several divided doses throughout the day or preferably in a single administration, in order to achieve the desired hematic level. Obviously it is at the discretion of the physician to adjust the quantity of product to be administered according to the age, weight and general conditions of the patient.

The medicament, e.g. in the form of a pharmaceutical composition, according to this invention can be prepared according to known methods in the art. The preferred route of administration is the oral one, however leaving alternative routes of administration, such as the parenteral route, to the discretion of the physician.

The following examples illustrate preferred formulations for oral administration, but do not intend to limit the invention in any way.

Gelatin capsules

According to known pharmaceutical techniques, capsules having the composition below and containing 1 g of active ingredient (EPA + DHA, 85% titer) per capsule are prepared.

Formulation 1

EPA-ethyl ester	525 mg/capsule;
DHA-ethyl ester	315 mg/capsule;
d-alpha tocopherol	4 IU/capsule;
gelatin	246 mg/capsule
glycerol	118 mg/capsule;
red iron oxide	2.27 mg/capsule;
yellow iron oxide	1.27 mg/capsule

Formulation 2

Ethyl esters of poly-unsaturated fatty acids with content in ethyl esters of ω-3 poly-unsaturated esters (eicosapentaenoic EPA , docosahexaenoic (DHA)	1000 mg 850 mg
d-1-α tocopherol	0.3 mg
gelatin succinate	233 mg
glycerol	67 mg
sodium p-oxybenzoate	1.09 mg
sodium propyl p-oxobenzoate	0.54 mg

CLAIMS

1. Use of essential fatty acids containing a mixture of eicosapentanoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction where the content in EPA+DHA in such mixture is greater than 25% b.w.

2. Use according to claim 1, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

3. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

4. Use according to claim 1 or 2, wherein the content in EPA+DHA in such mixture is about 85% b.w.

5. Use according to anyone of claims 1 to 4, wherein the medicament is for oral administration.

6. Use according to claim 4, wherein the medicament is for oral administration, at a dosage from about 0.7 g to about 1.5 g daily.

7. Use according to claim 6, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

8. Use of essential fatty acids containing eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) in the preparation of a medicament useful for preventing mortality in a patient who has suffered from a myocardial infarction, wherein the EPA or DHA content is greater than 25% b.w.

9. Use according to claim 8, wherein the medicament is useful for preventing mortality due to sudden death in a patient who has suffered from a myocardial infarction.

10. Use according to claim 8 or 9, wherein the EPA or DHA content is from about 60 to about 100% b.w.

11. Use according to anyone of claims 8 to 10, wherein the medicament is

for oral administration.

12. A method for preventing mortality in a patient who has survived a myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (EPA) and docosahexaenoic acid ethyl ester (DHA) wherein the content in EPA+DHA in such mixture is greater than 25% b.w.

13. A method according to claim 12, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

14. A method according to claim 12, wherein the content in EPA+DHA in such mixture is about 85% b.w.

15. A method according to claim 12, 13 or 14, wherein the medicament is administered orally.

16. A method according to claim 14, wherein the medicament is administered orally at a dosage from about 0.7g to about 1.5 g daily.

17. A method according to claim 16, wherein the EPA/DHA ratio in the EPA+DHA mixture is about 0.9/1.5

18. A method for preventing sudden death in a patient, who is survivor of myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids containing a mixture of eicosapentaenoic acid ethyl ester (DPA) and docosahexaenoic acid ethyl ester (DHA), wherein the content in EPA+DHA in such mixture is greater than 25% b.w.

19. A method according to claim 18, wherein the content in EPA+DHA in such mixture is from about 30 to about 100% b.w.

20. A method according to claim 18, wherein the content in EPA+DHA in such mixture is about 85% b.w.

21. A method according to claim 18,19 or 20, wherein the medicament is

administered orally.

22. A method according to claim 20, wherein the medicament is administered orally at a dosage from about 0.7g to about 1.5 g daily.

23. A method according to claim 22, wherein the EPA/DHA ration in the EPA+DHA mixture is about 0.9/1.5.

24. A method for preventing morality in a patient who has survived a myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or in docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

25. A method according to claim 24, wherein the contention EPA or DHA is form about 60 to about 100% b.w.

26. A method according to claim 24 or 25, wherein the medicament is administered orally.

27. A method for preventing sudden death in a patient who is survivor of myocardial infarction, comprising administering to said patient a therapeutically effective amount of a medicament containing essential fatty acids with a content in eicosapentaenoic acid ethyl ester (EPA) or docosahexaenoic acid ethyl ester (DHA) greater than 25% b.w.

28. A method according to claim 27, wherein the content in EPA or DHA is from about 60 to about 100% b.w.

29. A method according to claim 27 or 28, wherein the medicament is administered orally.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/23 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 760 081 A (A.LEAF, H.HALLAQ) 2 June 1998 (1998-06-02) claims 1,2,4 column 1, line 16-24 column 2, line 12-14 column 5, line 20-28 column 7, line 56-61 column 8, line 9-14 --- -/--	1,2,8,9, 12,18, 24,27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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